II. Withdrawal of Sequence Requirement

The December 2002 Action states that there is a difference between the sequence set forth in Figure 1 and that set forth in SEQ ID NO:5. In this regard, the Action notes that Figure 1 as filed shows a L (designating a "Leucine") at position 21, whereas SEQ ID NO:5 shows an Isoleucine. The Action imposes a requirement to comply with the sequence rules by submitting a sequence listing and includes a Notice to Comply.

In a voice mail message left for the Examiner, the undersigned counsel called the Examiner's attention to Applicants' Communication Under 37 C.F.R. §§1.821-1.825 and Amendment dated August 3, 2001. That Communication noted the discrepancy between SEQ ID NO:5 and Figure 1, indicated that the correct residue, as shown in GenBank, is Isoleucine, and indicated that correction of the formal drawing would follow at an appropriate time. The Examiner agreed, in a voice mail message left for the undersigned on April 1, 2003, that if a corrected Figure 1 was submitted, it would obviate the need for a new sequence listing. Thus, the corrected Figure 1 which accompanies this Amendment obviates both the sequence listing requirement and the Notice to Comply.

III. The Present Amendment

No new matter has been added by the present amendment.

The amendments to the claims add the recitation that the antibodies are anti-mesothelin antibodies, as requested by the Examiner.

The correction to Figure 1 changes the "L" at position 21 to "I". The correction is supported by page 41, lines 10-11, indicating that the nucleotide sequence encoding the amino acid sequence set forth in the Figure was deposited in GenBank under accession AF035617. A review of that accession reveals that the sequence encodes a "L"at position 21.

IV. The Rejections, and Responses Thereto

The Action withdraws all prior rejections under 35 U.S.C. §112, second paragraph, withdraws some rejections under §112, first paragraph, and withdraws all previous art rejections. The Action still, however, rejects the claims on several grounds. The various rejections are addressed in turn below. Applicants amend in part and traverse all the rejections.

A. Rejection of claims under 35 U.S.C. §112, first paragraph

The Action maintains the rejection of claims 113-121 and 123-144 under §112, first paragraph as not enabling a person of skill in the art to make and use the invention as claimed. According to the Action, the claims in question "do not recite the antigen to which the antibody binds to or for claims 135 and 140 which heavy or light chain to pair with the light and heavy chain to obtain an antigen binding pair because the antigen is not recited." Action, at page 5. Applicants amend in part and traverse.

1. Application of the rejection to claim 113

Applicants respectfully observe that the stated grounds do not support an enablement rejection. The antibody of claim 113 as presented contains complementarity determining regions ("CDRs") as set forth in Figure 1. It has been known in the art since at least the early 1990s that the CDRs determine antigen binding. Thus, the claimed antibodies have a defined binding specificity and the person of skill is enabled by the claim as presented to make and use the invention as claimed. What the Action seems to be concerned about is the claim does not on its face state what antigen it binds to. While true, that does not bear on whether the person of skill could make and use it - the antibody will still bind to whatever antigen is recognized by the CDRs. As the MPEP reminds the Examining Corps: "Office personnel must always remember to use the perspective of one of ordinary skill in the art. Claims and disclosures are not to be read in a vacuum." MPEP §2106 at page 2100-8 (8th ed., rev. 1, Feb. 2003). Given that the application is entitled "antibodies . . . having high binding affinity for mesothelin," it is difficult to see how one of skill in the art would have any confusion about the coverage of the claims.

Notwithstanding the foregoing, to expedite prosecution, claim 113 has been amended to recite that it is an anti-mesothelin antibody. Since the claim is a composition claim, Applicants understand the composition claimed to encompass any antibody with the CDRs shown in Figure 1. Accordingly, they do not understand or intend that the amendment to claim 113 changes its scope. Applicants also note for the record that the amendments are not made to overcome any art; no equivalents of the invention are or are intended to be surrendered.

2. Rejection as applied to claims 135 and 140.

As noted, the Action contends that claims 135 and 140 and the claims dependent thereon are not enabled because the claims do not recite the antigen to which the antibody binds and for claims 135 and 140 would not know "which heavy or light chain to pair with the light and heavy chain to obtain an antigen binding pair because the antigen is not recited." Action, at page 5. Applicants amend in part and traverse.

The rejection is based on an incorrect premise. The rejection assumes that a second chain must be paired with a heavy or light variable chain of the invention "to obtain an antigen binding pair." Applicants have already pointed out that this is incorrect. As noted in the Amendment dated October 22, 2002, the Patent and Trademark Office has officially recognized in U.S. Patent 5,980,895 that a single variable chain is sufficient to provide antigen-specific binding. See, October 22, 2002 Amendment at pages 17-18. Moreover, that Amendment pointed out that the results discussed in the '895 patent had been published by inventor Pastan in the Proceedings of the National Academy of Sciences in Kuan and Pastan, PNAS (USA) 93:974-978 (1996). A copy of the Kuan and Pastan PNAS article was provided with the October 22, 2002 Amendment. As set forth in the Kuan and Pastan PNAS paper, and in the '895 patent, there is no need for one of skill to pair a heavy or light chain of the invention to obtain an antigen binding pair, as assumed by the Action. Accordingly, the claims are correct as stated.

The remainder of the rejection does not support an enablement rejection. As discussed in the preceding section with regard to claim 113, the antibody of claims 135 and 140 as presented contain complementarity determining regions ("CDRs") as set forth in Figure 1. And, as discussed above, it has been known in the art since at least the early 1990s that the CDRs

determine antigen binding. Thus, the claimed antibodies have a defined binding specificity and the person of skill is enabled by the claim as presented to make and use the invention as claimed. As with the rejection of claim 113, above, what the Action seems to be concerned about is the claim does not on its face state what antigen it binds to. While true, that does not bear on whether the person of skill could make and use it - the antibody will still bind to whatever antigen is recognized by the CDRs. As the MPEP reminds the Examining Corps: "Office personnel must always remember to use the perspective of one of ordinary skill in the art. Claims and disclosures are not to be read in a vacuum." MPEP §2106 at page 2100-8 (8th ed., rev. 1, Feb. 2003). Given that the application is entitled "antibodies . . . having high binding affinity for mesothelin," it is difficult to see how one of skill in the art would have any confusion about the coverage of the claims.

Notwithstanding the foregoing, to expedite prosecution, claims 135 and 140 have been amended to recite an anti-mesothelin antibody. Since the claim is a composition claim, Applicants understand the composition claimed to encompass any antibody comprising a variable heavy chain with the CDRs shown in Figure 1 (claim 135) or a variable light chain with the CDRs shown in Figure 1 (claim 140). Accordingly, they do not understand or intend that the amendment to claims 135 or 140 change the scope of these claims. Applicants also note for the record that the amendment is not made to overcome any art; no equivalents of the invention are or are intended to be surrendered.

B. Rejection of the Claims As Not Reflecting Possession of the Invention

Claims 113-121 and 123-165 are rejected under §112, first paragraph as containing subject matter not described in the specification in such a way as to convey possession of the subject matter. According to the Action, the claims recite "Figure 1 (SEQ ID NO:5)". The Action notes that the recitation of SEQ ID NO:5 relates to GenBank Accession AF 035617. The Action asserts that it is not clear when this accession was placed in GenBank or whether the sequence originally deposited has been replaced. Action, at page 6. The Action invites clarification of the record as to the deposit of the "DNA" of the accession. *Id.* Applicants traverse.

Attached as Attachment 1 to this Amendment is a printout of an email forwarded to the undersigned by Dr. Ira Pastan, forwarding a message from Dr. Karen Clark of the GenBank Submissions Staff to one of the inventors, Dr. Chowdhury. Dr. Chowdhury had asked whether the submission accorded accession number AF035617 had been changed. Dr. Clark's reply states:

> "It appears that we received your submission on Nov 24, 1997. Before the record was processed, you sent in a sequence update on Dec 1, 1997: update_notes = The 61 st. nucleitide [sic] is A not T. This change was incorporated into your record during its processing. Your PNAS paper was added to the record in Sept. 1999."

Accordingly, the GenBank sequence shown under Accession No. AF035617 was changed to the sequence set forth in SEQ ID NO:5 on December 1, 1997, which is the date of filing of the application from which priority is claimed. The change made on December 1 changed the nucleotide at position 61 to A, which results in the change of the residue encoded at position 21 from "L" to "I", as recited in SEQ ID NO:5 and as shown in the corrected Figure 1 submitted with this Amendment. The sequence set forth in SEQ ID NO:5 was therefore deposited in GenBank as of the priority date of the application.

Applicants therefore had possession of the invention as claimed as of the priority date. Reconsideration, and withdrawal of the invention are respectfully requested

C. Rejection of Claim 120 under §112, first paragraph

Claim 120 is rejected under §112, first paragraph, as containing subject matter not described in the specification in such a way as to convey possession of the subject matter. According to the Action, the claim recites a dsFv having a VL and a VH having cysteines at recited positions. The Action notes that support for the recitation was stated by the Applicants to be found at page 8, lines 24-5 with the incorporation of US Patent 6,147,203. The Action states that the incorporation covers generic dsFv fragments, but not cysteines at specific locations and concludes that there is no support for a dsFv with cysteines at the specified locations. Action, at page 7. Applicants traverse.

The rejection is founded on the premise that the incorporation of application 08/077,252 (the "'252 application") is limited to a generic statement of dsFv fragments. This is an incorrect reading. The statement of incorporation of the '252 application does not refer to, for example, a specific page and paragraph that refers only to dsFv fragments in general, but to the entire application. The entirety of the specification of the '252 application, including the designation of particular residues that can be mutated to cysteines, therefore has always legally been part of the present specification.

This reading is consonant with the incorporations by reference of other applications in the same paragraph of the specification. For example, immediately after the incorporation of the '252 application, the specification states that the term "antibody" also includes "pFv fragments (See, U.S. Provisional Patent Applications 60/042,350 and 60/048,848, both of which are incorporated by reference.)." Specification, at page 8, line 25-27. By the Action's logic, this is just a generic reference to "pFv fragments." But the incorporation of the applications is manifestly of the entirety of the applications.

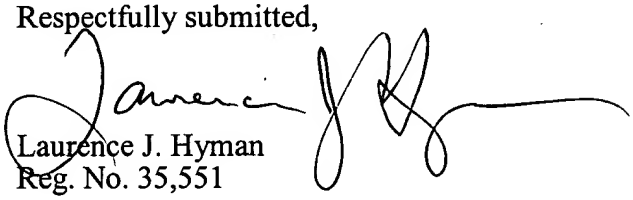
By contrast, the Action provides no analysis or reasoning supporting its contention that the incorporation by reference is of just generic dsFv fragments per se. The Action's contention is not consonant with the recitation of incorporations found at page 8 of the specification. The rejection should be reconsidered and, upon reconsideration, withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, he is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



Laurence J. Hyman
Reg. No. 35,551

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
LJH:ljh
SF 1463854 v1

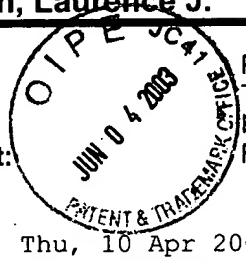
MARKED-UP VERSION SHOWING CHANGES

113. (Twice amended) An isolated anti-mesothelin antibody comprising a variable heavy (V_H) chain and a variable light ("V_L") chain, which V_H and V_L chains have complementarity-determining regions ("CDRs") as set forth in Figure 1 (SEQ ID NO:5).

135. (Twice amended) An isolated anti-mesothelin antibody comprising a variable heavy ("V_H") chain which V_H chain has complementarity-determining regions as set forth in Figure 1 (SEQ ID NO:5).

140. (Twice amended) An isolated anti-mesothelin antibody comprising a variable light ("V_L") chain which V_L chain has complementarity-determining regions as set forth in Figure 1 (SEQ ID NO:5).

Hyman, Laurence J.



From: Pastan, Ira [pastani@pop.nci.nih.gov]
Sent: Thursday, April 10, 2003 1:56 PM
To: Hyman, Laurence J.
Subject: Fwd: [NCBI_REF 354635] GenBank AF035617 reply

>Date: Thu, 10 Apr 2003 16:34:20 -0400 (EDT)
>From: gb-admin@ncbi.nlm.nih.gov
>Reply-To: gb-admin@ncbi.nlm.nih.gov
>To: partha@helix.nih.gov, pastani@pop.nci.nih.gov
>Cc: chowdh@vetmail.trotnet.vet.ksu.edu, partha_chowdhury@hgsi.com
>Subject: [NCBI_REF 354635] GenBank AF035617 reply
>X-Virus-Scanned: by amavisd-milter (http://amavis.org/)
>
>Dear Dr. Chowdhury,
>
>In response to your recent request:
>
>>I had submitted a nucleotide sequence to GenBank in 1997. The accession
>>number for the sequence is AF035617. I have the following two questions
>>pertaining to this submission.
>>(1) Was any change made in the original submission at a later date?
>>(2) If a change was made what was it when was that done?
>
>It appears that we received your submission on Nov 24 1997. Before the
>record was processed, you sent in a sequence update on Dec 1 1997:
>
>>update_notes = The 61 st. nucleitide is A not T.
>
>This change was incorporated into your record during its processing.
>Your PNAS paper was added to the record in Sept. 1999.
>
>
>Sincerely,
>
>Karen Clark, PhD
>The GenBank Submissions Staff
>Bethesda, Maryland USA
>**
>(301) 496-2475
>(301) 480-2918 fax
>gb-admin@ncbi.nlm.nih.gov (for replies/updates to entries in GenBank)
>info@ncbi.nlm.nih.gov (for general questions regarding GenBank)
>**
>
>GenBank flatfile:
>
>
>LOCUS AF035617 723 bp mRNA linear ROD
>30-SEP-1999
>DEFINITION Mus musculus scFv antibody SS mRNA, partial cds.
>ACCESSION AF035617
>VERSION AF035617.1 GI:2921393
>KEYWORDS .
>SOURCE Mus musculus (house mouse)
> ORGANISM Mus musculus
> Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
> Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
>REFERENCE 1 (bases 1 to 723)
> AUTHORS Chowdhury,P.S., Viner,J.L., Beers,R. and Pastan,I.
> TITLE Isolation of a high-affinity stable single-chain Fv specific for
> mesothelin from DNA-immunized mice by phage display and
> construction of a recombinant immunotoxin with anti-tumor activity

> JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 95 (2), 669-674 (1998)
> MEDLINE   98118570
> PUBMED   9435250
>REFERENCE   2 (bases 1 to 723)
> AUTHORS   Chowdhury,P.S.
> TITLE   Direct Submission
> JOURNAL   Submitted (24-NOV-1997) LMB, NCI, 37 Convent Drive, Bld. 37 Rm.
>   4B20, Bethesda, MD 20892-4255, USA
>FEATURES   Location/Qualifiers
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>   /strain="Balb/c"
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>   /clone_lib="phage display library made from
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>   mice immunized with DNA"
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>BASE COUNT   176 a   180 c   203 g   164 t
>ORIGIN
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>   61 atatcctgca aggcttctgg ttactcattc actggctaca ccatgaactg ggtgaagcag
>   121 agccatggaa agagccttga gtggattgga cttattactc cttacaatgg tgcttctagc
>   181 tacaaccaga agttcagggg caaggccaca ttaactgtag acaagtcatc cagcacagcc
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>   661 tactgccagc agtggagtgg ttaccctctc acgttcggtg ctgggacaaa gttggaaata
>   721 aaa
>//

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Please note my new email address is pastani@pop.nci.nih.gov
Ira Pastan, M.D.
Chief, Laboratory of Molecular Biology
37 Convent Drive MSC 4264 Bld 37 5106
Bethesda, Maryland 20892-4264
National Cancer Institute
National Institute of Health
Phone: (301) 496-4797
Fax: (301) 402-1344